REMARKS

Applicants have amended Claim 1 and added Claim 13. Support for the amended claims and newly added claims can be found throughout the specification and claims as originally filed, for example in Paragraph **[0150]**. As such, no new matter has been added.

35 U.S.C. §112, Paragraph 1

The Examiner has rejected Claims 76-87 under 35 U.S.C. §112, ¶1, asserting that the claims do not provide reasonable enablement for the claimed methods. The Examiner notes that the preamble of Claim 76 recites "[a] method of producing definitive endoderm" whereas the active step of the claim recites "obtaining a cell population comprising pluripotent human cells." The Examiner asserts that the claimed method is not enabled for producing any mammalian species definitive endoderm cells other than human definitive endoderm cells. Although Applicants submit that it is implicit in the claim that the definitive endoderm cells produced through practicing the claims are human definitive endoderm, in order to expedite prosecution of the application Applicants have amended Claim 76 to recite production of "human definitive endoderm." Accordingly, the Examiner's objection has been traversed.

The Examiner further asserts that the pluripotent mammalian cell recited in claim 1 reads on induced pluripotent stem cells (iPS), which have not been demonstrated to "behave in an identical way as pluripotent stem cells." Applicants respectfully disagree. *Yu et al.* (Human Induced Pluripotent Stem Cells Free of Vector and Transgene Sequences, Science, 324:797-801 (2009)) demonstrate that iPS cells possess the same features as human ES cells that distinguish them from other cell types. Furthermore, Yu et al. demonstrate that iPS cells can differentiate into cell types of the three germs layers both *in vitro* and *in vivo*. Specifically, Yu et al., states:

> These iPS cell colonies exhibited typical human ES cell morphology (e.g., compact colonies, high nucleus-to-cytoplasm ratios, and prominent nucleoli) (Fig. 1B) and exhibited gene expression profiles that were very similar to those of the parental fibroblasts (Fig. 1C and table S3). Similar to human ES cells, when injected into immunocompromised mice, these iPS cells formed teratomas consisting of differentiated derivatives of all three primary germ layers (Fig. 1D). ... The iPS cell subclones were morphologically similar to human ES cells (Fig. 3A); had normal karyotypes (Fig. 3B); expressed human ES cell-specific cell surface markers (Fig. 3D) and genes (Fig. 4, A and B, fig. S4, and table S4); and

> differentiated into derivatives of all three germ layers in teratomas (Fig. 4C) (emphasis added; Yu et al. at 799-800)

Yu et al. also demonstrate that iPS cells "behave in an identical way to pluripotent stem cells" as indicated in the claims. Also, *Zhang et al.* demonstrate that iPS cells can be differentiated into insulin-producing cells using the same step-wise protocol used for hES cells. *Zhang et al.*, Highly Efficient Differentiation of Human ES Cells and iPS Cells into Mature Pancreatic Insulin-Producing Cells. Cell Research (2009) 19:429-438 (enclosed herewith for the Examiner's convenience).

The Examiner also asserts that the specification of the instant application does not contemplate the use of iPS cells as a species of pluripotent cells that can be used to practice the claimed method. The Examiner thus alleges that the claims lack enablement. Applicants respectfully disagree.

It is well-established that an inventor need not describe every potential type of material that can be utilized in a claimed method. The fact that later developed materials can be used in connection with a claimed process without undue experimentation is well reflected in section 2164.08 of the MPEP as well as current case law. For example, in *In re Goffe* the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In re Goffe, 542 F.2d 564, 567 (CCPA 1976). The proper inquiry is not whether the material existed at the time the specification was filed, but rather, whether a skilled artisan would be able to perform the steps of the method on the material so as to achieve the stated result without undue experimentation. As discussed above, human iPS cells have been shown to behave just as human ES cells in their ability to differentiate. Furthermore, human iPS cells have been shown to be responsive to signaling factors in the same way as human ES cells. As such, it is clear that

a skilled artisan could practice the claimed method using iPS cells without undue experimentation.

In addition to the foregoing, the Examiner contends that one of skill in the art require undue experimentation to make and use the claimed invention commensurate in scope with the claims 76-87 because the specification allegedly does not provide enabling support for providing the cell population with any TGF-β superfamily growth factor or with any Wnt-pathway activator. Applicants respectfully disagree.

Applicants respectfully submit that a skilled artisan would not require undue experimentation in selecting a TGF-β superfamily growth factor so as to initiate differentiation as set forth in the claims. Currently, there are approximately 33 agents known to interact with a TGF-β receptor family member. The Examiner has already acknowledged that the specification demonstrates that activin A is an agent capable of differentiation of hES cells to human definitive endoderm. In addition, Applicants provide herewith is a Declaration under 37 C.F.R. §1.132 by Dr. Kevin D'Amour, which demonstrates that activin B, GDF8, and GDF11 are three additional agents capable of inducing definitive endoderm cells from human embryonic stem cells as recited in independent Claim 76. Thus, Applicants have shown that at least 4 agents can activate a TGF-β receptor family member and induce differentiation of hES cells to human definitive endoderm cells. Furthermore, this declaration demonstrates that TGF-β 1, TGF-β 2, TGF-β 3, GDF3, GDF9 and GDF15 are not capable of activating a TGF-β receptor family member so as to initiate differentiation of human embryonic stem cells to human definitive endoderm cells under the claimed conditions. As such, Applicants have tested nearly a third of the known TGF-β superfamily growth factors and have demonstrated that about half of the factors tested promote the differentiation of hES cells to human definitive endoderm cells. The remaining TGF-β superfamily growth factors can easily be tested by a skilled artisan without undue experimentation in view of the guidance provided in the specification.

For example, the instant specification in Example 6 provides detailed instructions which enable a skilled artisan to use routine methods to test TGF-β superfamily growth factors so as to distinguish those that are capable of initiating differentiation of hES cells to definitive endoderm cells from ones that cannot initiate such differentiation. Moreover, just as TGF-β superfamily growth factors can easily be tested by a skilled artisan without undue experimentation in view of

the guidance provided in the specification, so too can the Wnt pathway activators in combination with the TGF-β superfamily growth factors. Accordingly, Applicants respectfully submit that the specification is sufficient to enable one skilled in the art to make and/or use the full scope of the claimed invention without undue experimentation.

Applicants would also like to point out that a claim does not lack enablement simply because it encompasses non-working embodiments (see section 2164.08(b) of the MPEP). Rather, "[t]he standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). As discussed above, in view of the guidance in the specification, it would require no more than routine experimentation for a skilled artisan to determine which factors promote differentiation of hES cells to definitive endoderm cells and those factors that do not.

Finally, the Examiner contends that the specification does not provide enabling support for providing serum at any concentration for initial culture of pluripotent human cells other than initially providing serum at a low concentration to said cell population. Applicants respectfully disagree.

The Examiner does not point to any evidence suggesting that the presence of insulin at a concentration at or above 0.2 μg/ml would render the method of Claim 76 inoperable. As noted by the Examiner, *McLean et al.* point out that contacting human embryonic stem cells with insulin in a concentration as little as 0.2 μg/ml during the differentiation process is detrimental to the production of definitive endoderm. *McLean et al.* do not, however, state that the presence of insulin would eliminate the differentiation of pluripotent cells to human definitive endoderm. Claim 76 merely lays out a method for the differentiation of pluripotent cells to human definitive endoderm and does not recite the efficiency of the differentiation process or a requisite number of definitive endoderm cells produced by the claimed method. Applicants respectfully submit that even if the practice of the method detailed in Claim 76 resulted in the differentiation of only a single pluripotent cell to definitive endoderm, the claim would still be fully enabled. Applicants respectfully submit that Claim 76 covers the breadth of the fully enabled process that is an embodiment of the invention. As the Examiner has not met his burden of establishing that

the process recited in Claim 76 would not result in the differentiation a human pluripotent cell to human definitive endoderm, Applicants respectfully request withdrawal of the rejection and placement of the claim in condition for allowance.

35 U.S.C. §102(e)

The Examiner has rejected Claims 76, 77, 79, 80, and 82-87 under 35 U.S.C. §102(e) as allegedly anticipated by *Fisk et al.* (U.S. Patent No. 7,326,572) as evidenced by *Kuo et al.*

Applicants respectfully submit that *Fisk et al.* fail to teach all of the elements of any claim, and therefore, none of the claims are anticipated. For example, *Fisk et al.* fail to teach "providing said cell population with a TGFβ superfamily growth factor and a Wnt-pathway activator." *Fisk et al.* do not disclose a Wnt-pathway activator. The Examiner notes, however, that *Fisk et al.* disclose n-butyrate. The Examiner then contends that because *Kuo et al.* state that n-butyrate is a histone deacetylase inhibitor it non-specifically activates transcription, and therefore, it must activate the Wnt-pathway. Applicants respectfully disagree.

The Examiner's argument relies on the doctrine of inherent anticipation. In particular, the Examiner contends that because n-butyrate is inherently a non-signal-specific transcriptional activator, it must activate the Wnt-pathway, and therefore, the disclosure of n-butyrate anticipates the instant claims. However, it is clear that **inherency may not be established by probabilities or possibilities**. *Scaltech v. Retec/Tetra, L.L.C.*, 178 F.3d 1378 (Fed Cir. 1999), *emphasis added.* The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *Id.* (citations omitted). The Examiner contends that inhibition of histone deacetylase by n-butyrate is known to activate transcription of genes in mammalian genome. This does not establish that n-butyrate would activate the Wnt pathway. It is mere speculation that the general activation of transcription of genes in the mammalian genome could potentially result in heightened activation of the Wnt pathway. Using this logic, it is also possible that general activation of the mammalian genome could just as well result in transcription of a factor that inhibits the Wnt pathway. It is, at best, unclear. The Examiner's argument is thus impermissibly based on the probability or possibility of n-butyrate acting as a Wnt-pathway activator. Accordingly, the Examiner has not met the burden of establishing that independent claim 1 or any of the claims dependent thereon are anticipated under 35 U.S.C.

§ 102. Because *Fisk et al.* fail to teach all of the elements of any claim, Applicants respectfully request withdrawal of the Examiner's rejection and placement of the case in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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